Relationship between serum ferritin and endocrinopathies in thalassemic children: A hospital-based study

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Received - 31 March 2019 Initial Review - 29 April 2019 Accepted - 01 May 2019

ABSTRACT

Background: Thalassemia syndromes are a heterogeneous group of Mendelian disorders characterized by lack of/decreased synthesis of either α/β globin chains of hemoglobin. It results in ineffective erythropoiesis and lysis of mature red blood cells in the spleen. Thalassemic patients require multiple blood transfusions which led to iron overload. **Objective:** This study evaluated endocrinopathies in thalassemic patients of age 5–18 years and relationship with serum ferritin level. **Materials and Methods:** This is a hospital-based cross-sectional study on 70 transfusion dependent thalassemic children of 5–18 years attending the department of pediatrics, of a tertiary care hospital in Assam. Their height, sexual maturity rating, serum ferritin, calcium, alkaline phosphatase, phosphate, thyroid stimulating hormone, random blood sugar, and fasting blood sugar were recorded. The data were analyzed statistically and $p < 0.05$ was considered to be statistically significant. **Results:** The study population (70) consisted of 40 males and 30 females. In this study, 91.67% (22 of 24 cases) had delayed puberty, 50% (35 of 70) were stunted, 37.14% (26 of 70 cases) were hypocalcemic, 31.43% (22 of 70) had hypothyroidism, and 2.85% (2 of 70) were diabetic. The mean serum ferritin level was 2845±859.40 ng/ml in delayed puberty while it was 2027.50±21.92 ng/ml ($p > 0.05$) in thalassemic children with normal puberty. The mean serum ferritin in stunted thalassemic children was 2909.86±820.93 ng/ml and it was 1421.43±283.41 ng/ml ($p < 0.001$) in normal height thalassemics. The mean serum ferritin in hypothyroid thalassemics is 2806.59±929.57ng/ml and is 1885.75±846.89 ng/ml ($p < 0.001$) in euthyroid cases. The mean serum ferritin in diabetic thalassemics was 2772.50±1092.48 ng/ml and it was 2147.16±965.63 ng/ml ($p > 0.05$) in nondiabetic thalassemics. **Conclusion:** Growth retardation and endocrinal complications significantly occur in transfusion-dependent thalassemic children. Adequate chelation therapy helps in controlling serum ferritin levels thereby enabling chronically transfused thalassemic children to grow normally without early endocrinal complications.

Key words: *Chelation, Endocrinopathies, Serum ferritin, Thalassemia*

Thalassemias are a heterogeneous group of disorders recessively inherited with a genetically determined reduction in the rate of synthesis of one or more types of normal hemoglobin (Hb) polypeptide chains. It is the most common monogenic disease [1,2]. All over the world, around 100,000 children are born each year with severe homozygous state of thalassemia. Thalassemia belt stretches across the African continent, Mediterranean regions, Middle East, Indian subcontinent, Southeast Asia, Southern China, and Malaysia [1]. In India, over 20 million people have the thalassemia gene. The prevalence of β genes varies from 3% to 18% in the north and 1–3% in the south. Different states of the North Eastern region show a variable incidence of HbE varying from 16.2% to 47.3% [3-5]. A huge migrant tea garden population shows a high incidence of HbS [6].

Although the benefits of regular red blood cells transfusions in patients are increasingly recognized, this approach also has the clinical consequence of iron overload, often presenting as a secondary disease among transfusion-dependent patients. Iron overload, for a long time, has been considered to be the major cause of endocrine abnormalities of β thalassemia and this is supported by histological studies of different endocrine glands [7-9].

Growth disturbances are a major clinical feature of untreated patients with thalassemia [10]. The increasing mean survival age is indicative of the fact that modern therapies are generally safe and effective but it is becoming increasingly clear that as thalassemic patients approach the age of puberty, many of them develop growth retardation [11]. It is generally believed that growth retardation is directly related to iron toxicity, especially of endocrine glands [12,13].

Primary hypothyroidism that may affect thalassemic patients from the second decade of life is mainly due to gland infiltration by iron overload. Diabetes mellitus in patients receiving hypertransfusion for thalassemia is usually attributed to damage to β cells due to iron deposition and has been assumed to be the principal cause of insulin deficiency. The insulin resistance

has been postulated to be at the level of the liver (due to iron deposition), where it may interfere with the insulin's ability to suppress hepatic glucose uptake and also at the level of the muscle where iron deposits may decrease the glucose uptake [14].

Studies regarding endocrinopathies in thalassemic children in this part of the country are limited. Hence, the present study was undertaken to study the endocrinal complications of thalassemic children of age group 5–18 years and to find out the relationship between serum ferritin level and endocrinal complications.

MATERIALS AND METHODS

This was a hospital-based cross-sectional study carried out over 12 months from June 2017 to –May 2018 in the department of pediatrics, of a tertiary care hospital, Assam. The study was conducted with approval from the Institutional Ethics Committee. All children in the age group 5–18 years attending the department of pediatrics, who were diagnosed with transfusion-dependent thalassemia (beta-thalassemia major, HbE beta-thalassemia, and HbS beta-thalassemia) and fulfilling the inclusion criteria, were enrolled. After verifying the records, informed consent was taken from the parents and those children who fulfilled the inclusion criteria.

Data regarding age, gender, ethnic group, socioeconomic status, age at diagnosis, type of hemoglobinopathy, presenting clinical features, and duration of chelation therapy were recorded in a predesigned pro forma. Detailed clinical examination and anthropometry were performed. Blood obtained by venipuncture and collected in clot activated vials for serum ferritin (ELISA), calcium, alkaline phosphatase, phosphate, thyroid-stimulating hormone (TSH) (Immunoradiometric assay) and in fluoride vials for random blood sugar, and fasting blood sugar (after 6 h of fasting).

We used the following definition to define our cases: Stunting: Height was measured by stadiometer by standard method. WHO chart for height for age was used as reference standard. Height for age between −2 standard deviation (SD) and −3 SD was considered moderate stunting and <−3SD was considered severe stunting (WHO). Diabetes mellitus: Thalassemic children whose random plasma glucose was ≥200 mg/dl (on two separate occasions) or fasting plasma glucose was ≥126 mg/dl on two occasions were considered diabetic [15]. Hypothyroidism: Thalassemic children with TSH > 5.5 m IU/L were considered to be having hypothyroidism [16]. Hypogonadism: Absence of testicular enlargement in boys, not increasing from 2 ml to more than 4 ml as measured by Prader orchidometer (14 years in boys) or breast development in girls at an age that is 2–2.5 SD later than the population mean (13 years in girls) is hypogonadism [17]. Hypocalcemia: Total Serum calcium <9 mg/dl [18]. Hyperphosphatemia: Serum phosphorous >5.6 mg/dl (5-11 years), >5.4 mg/dl (12-15 years), >4.7 mg/dl (16-18 years) [19].

Data were analyzed using Microsoft Excel 2007. Data were presented as mean±SD or percentage. $p<0.05$ was considered as statistically significant. All the statistical analysis was done with a 95% confidence interval. Statistical significance was tested using analysis of variance and unpaired t test.

RESULTS

The present study comprised 70 thalassemic children which were beta-thalassemia major (19, 27.14%), HbE beta-thalassemia (44, 62.86%), and sickle beta-thalassemia (7,10%). Among the study population, 58.58% were from lower socioeconomic status and 41.42% were from the lower middle class. The mean age of the children included in the study was 9.77±3.91 years (Table 1) with a male: female ratio of 1.33:1.

We found that most of the children had serum ferritin level between 1000 and 2000 ng/ml and mean was 2165.64±966.20 ng/ml (Table 2). Only 10 (14.29%) thalassemia children were on regular chelation (deferasirox). The mean serum ferritin in the thalassemic subjects who had not taken iron chelator was 2775.32±933.00 ng/ml and was significantly higher than those who had taken iron chelator either regularly or irregularly ($p<0.001$) (Table 3).

In our study, 50% (35) of thalassemic children were stunted which was more prominent after 9 years of age. Total 78.57% children in 9–12 years and 91.67% children in 13–18 years age group were stunted. On the contrary, only 6.25% of children between 5 and 8 years were stunted. The mean serum ferritin in stunted thalassemic children was 2909.86±820.93 ng/ml while it was 1421.43±283.41 ng/ml in normal height thalassemic subjects ($p<0.001$). The current study revealed that 13 out of 40 males

Table 1: Age distribution of thalassemic children

Age group (in years)	n (%)
5–8	32 (45.71)
9–12	14 (20.00)
13–18	24 (34.29)
Total	70 (100.00)
Mean±SD	9.77±3.91 years

Table 2: Level of serum ferritin in thalassemic children

Serum ferritin (ng/ml)	n (%)
<1000	1 (1.43)
1000–2000	36 (51.43)
>2000	33 (47.14)
Total	70 (100.00)
Mean±SD	2165.64±966.20

Table 3: Distribution of thalassemic children according to chelation therapy and mean serum ferritin level

Chelation therapy	n (%)	Ferritin level (mean±SD)	p-value
Not taken	31 (44.29)	2775.32±933.00	<0.001
Regularly taken	10 (14.29)	1210.00±237.81	
Irregularly taken	29 (41.42)	1843.45±710.26	
Total	70 (100.00)		

SD: Standard deviation

Table 4: Comparison of mean serum ferritin between thalassemic children with endocrinopathy and normal thalassemic children

Variable	Mean±SD	p-value
Stunted	2909.86±820.93	<0.001
Normal height thalassemic children	1421.43±283.41	
Delayed puberty	2845±859.40	>0.05
Normal puberty	2027.50±21.92	
Hypothyroid	2806.59±929.57	<0.001
Euthyroid	1885.75±846.89	
Hypocalcemic	3090.92±814.43	<0.001
Normocalcemic	1618.89±537.41	
Diabetic	2772.50±1092.48	>0.05
Nondiabetic	2147.16±965.63	

(32.5%) had delayed puberty and 9 out of 30 females (30%) had delayed puberty with a male: female ratio of 1.44:1. Table 4 compares the mean serum ferritin of thalassemic children (with endocrinopathy) and normal thalassemic children.

DISCUSSION

The Northeastern region of India, particularly Assam, is a rich reservoir of hemoglobinopathies and thalassemias due to the migration of various races over the ages and hence being home to an assortment of socio-cultural, linguistic, and ethnically diverse people. It has been shown by earlier authors that high gene frequency for HbE is prevalent in autochthonous inhabitants of Assam, having cultural and linguistic affiliation with the population of Southeast Asian countries. Whereas HbS is restricted to the tea garden labor communities, a group of population brought to Assam by British colonial tea planters from Central, Eastern, and Southern India during the mid-19th century.

In the present study, 31 (44.29%) children were not on any chelation therapy due to economic and other constraints. In our institution, we generally use deferasirox as an iron chelator. Only 39 (55.71%) were receiving chelation therapy, out of which, 10 children were on regular chelation therapy and rest 29 children were on irregular chelation therapy. Similar observations were found by Singhal *et al.* [20] where 47.6% of the cases were not on chelation therapy. Furthermore, Saxena *et al.* [21] reported in their study that only 20% of the patients were taking optimum chelation dose.

In this study, only 1 (1.43%) patient had serum ferritin <1000 ng/ml, 36 patients (51.43%) had serum ferritin value between 1000 and 2000 ng/ml and 33 (47.14%) had serum ferritin value >2000 ng/ml with mean serum ferritin 2165.64±966.20 ng/ml. The mean serum ferritin in thalassemic subjects in the age group of 5–8 years was 1535.94±596.65 ng/ml, in 9–12 years was 2557.14±993.90 ng/ml, and in 13–18 years was 2776.88±853.01 ng/ml. Hence, with the advancement of the age of the thalassemic subjects, there was a statistically significant increase in mean serum ferritin ($p<0.001$). We had found that mean serum ferritin value was significantly higher in cases who had not taken chelation therapy. Similar results were obtained in a study by Riaz *et al.* [22] where mean serum ferritin level increased progressively after 9 years of age.

In this study, we found that stunting was more prominent after 9 years of age with the mean age being 12.06±2.24 years. We noticed that the mean serum ferritin level of stunted thalassemic children was significantly higher than their counterparts with normal height ($p<0.001$). Similar results were obtained by Hamidah *et al*. [23] where they reported that the prevalence of impaired growth velocity among the transfusion dependent pre-pubertal thalassemics was 57.7% and short stature was more prevalent in those above 10 years old compared to those below 10 years old (83.3% and 16.7%, respectively). The mean serum ferritin value of the thalassemic children with short stature was higher compared to patients with normal height. Similar observations were made by Najafipour *et al.* [9] also. Delayed puberty was seen in 91.67% of the cases with the mean age being 14.36±1.09 years. In our study, 32.50% males and 30% of females had delayed puberty; the mean serum ferritin value of thalassemic patients with delayed puberty was higher than in patients with normal puberty. However, the difference in the mean serum ferritin level was not statistically significant between the two groups. Chhabra and Sodhi [24] concluded that hypogonadism was the most frequent endocrine complication in transfusion-dependent thalassemic children and the most common cause is iron overload. This finding is in accordance with the results of other investigators like Soliman *et al.* [25] mentioned that delayed puberty was frequent finding both in boys and girls with thalassemia. Berkovitch *et al.* [26] had found that 28 out of 33 thalassemia patients achieved normal puberty.

We found that hypothyroidism was present in 22 (31.43%) and the mean age of the hypothyroid thalassemic patients was 10.91±3.26 years. Drema *et al.* [27] reported hypothyroidism in 26% of their cases. As serum ferritin is the most widely used test for assessment of iron status in thalassemic patients, we found a statistically significant difference in mean serum ferritin level between euthyroid and hypothyroid groups in our study. Similar reports were replicated in studies by Pirinççioğlu *et al.* [28] and Jaipuria *et al.* [29]. The mean serum ferritin in hypocalcemic thalassemic cases was significantly higher (3090.92±814.43 ng/ml) than that in normocalcemic thalassemic cases (1618.89±537.41 ng/ml) ($p<0.001$). Joshi and Phatarpekar. [30] found that 37.7% of cases were hypocalcemic. We found 2.85% with diabetes mellitus and the mean age was 14.50±2.12 years. Sharma *et al.* [31] reported that 4.7% of the included patients had diabetes mellitus and there was no correlation between the serum ferritin levels of patients with and without diabetes. The mean serum ferritin in diabetic thalassemic cases was higher than in nondiabetic cases, but it was not statistically significant which could be due to immune system activation against pancreatic beta cells in addition to chronic iron overload.

Adding to the limitation of this study was the small sample size; the study included only 70 children as the study was limited to only those thalassemic children who seek services in pediatric medicine department of the tertiary care center. The study was conducted for a short duration of time. No, follow-up was done as the study was cross-sectional.

CONCLUSION

All thalassemic children should be monitored for detecting endocrine abnormalities annually. Proper and regular use of iron chelators should be started in all thalassemic children receiving blood transfusion for 1 year and if serum ferritin is >1000 ng/ml. In our study, the majority of the thalassemic children belonged to lower socioeconomic status and were unable to take iron chelators regularly due to financial constraint.

REFERENCES

1. Lokeshwar MR. Thalassemia syndromes. In: Parthasarathy A, editor. IAP Textbook of Pediatrics. 6th ed. New Delhi: Jaypee Brothers; 2016.
2. Lokeshwar MR. Management of thalassemia. In: Parthasarathy A, editor. Partha's Fundamentals of Pediatrics. 1st ed. New Delhi: Jaypee Brothers; 2007. p. 421.
3. Dash S, Chhanhimi L, Chhakchhuak L, Zomawaia E. Screening for haemoglobinopathies and G6PD deficiency among the mizos of mizoram: A preliminary study. Indian J Pathol Microbiol 2005;48:17-8.
4. De M, Halder A, Podder S, Sen R, Chakrabarty S, Sengupta B, *et al.* Anemia and hemoglobinopathies in tribal population of Eastern and North-Eastern india. Hematology 2006;11:371-3.
5. Das B, Sengupta S. RETRACTED: HbE genotypes and fertility: A study on a Tibeto-Burmese population in Upper Assam, India. Ann Hum Biol 2008;35:422-31.
6. Sharma S, Mahanta J. Prevalence of haemoglobin variants in malaria endemic Northeast India. J Biol Sci 2009;9:288-91.
7. Abdulzahra MS, Al-Hakeim HK, Ridha MM. Study of the effect of iron overload on the function of endocrine glands in male thalassemia patients. Asian J Transfus Sci 2011;5:127-31.
8. Mahmoodi M, De Sanctis V, Karimi M. Diffuse intracerebral calcification in a beta-thalassaemia major patient with hypoparathyroidism: A case report. Pediatr Endocrinol Rev 2011;8 Suppl 2:331-3.
9. Najafipour F, Aliasgarzadeh A, Aghamohamadzadeh N, Bahrami A, Mobasri M, Niafar M, *et al.* A cross-sectional study of metabolic and endocrine complications in beta-thalassemia major. Ann Saudi Med 2008;28:361-6.
10. Kattamis CA, Kattamis AC. Management of thalassemias: Growth and development, hormone substitution, vitamin supplementation, and vaccination. Semin Hematol 1995;32:269-79.
11. De Sanctis V, Katz M, Vullo C, Bagni B, Ughi M, Wonke B. Effect of different treatment regimes on linear growth and final height in β-thalassaemia major. Clin Endocrinol 1994;40:791-8.
12. Gabutti V, Piga A, Sacchetti L, Sandri A, Biginelli M, Saracco P, *et al.* Quality of life and life expectancy in thalassemic patients with complications. Prog Clin Biol Res 1989;309:35-41.
13. Merkel PA, Simonson DC, Amiel SA, Plewe G, Sherwin RS, Pearson HA, *et al.* Insulin resistance and hyperinsulinemia in patients with thalassemia major treated by hypertransfusion. N Engl J Med 1988;318:809-14.
14. Chern, J. Lin, K. Lu, M. *et al*. Abnormal glucose tolerance in transfusion-dependent-thalassemic patients. Diabetes Care 200;24:850-4.
15. Vijayalakshmi B. Diagnostic criteria for diabetes mellitus. In: Parthasarathy A, editor. IAP Textbook of Pediatrics. 6th ed. New Delhi: Jaypee Brothers; 2016. p. 921.
16. Franchi L. Thyroid function test. In: Kliegman ER, Stanton B, editors. Nelson Textbook of Pediatrics. 1st ed. South Asia: Elsevier India; 2015. p. 2670.
17. Shah SN, Sarathi V. Delayed puberty. In: Gupta P, Menon PS, editors. PG Textbook of Pediatrics. 1st ed. New Delhi: Jaypee Brothers; 2015. p. 2328.
18. Bagga A, Khandelwal P. Fluid, electrolyte and acid-base disorders. In: Srivastava RN, Bagga A, editors. Pediatric Nephrology. 6th ed. New Delhi: Jaypee Brothers; 2016. p. 88-127.
19. Greenbaum LA. Phosphorous metabolism. In: Kliegman ER, Stanton B, editors. Nelson Textbook of Pediatrics. 1st ed. South Asia: Elsevier India; 2015. p. 366.
20. Singhal B, Shama N, Mathur R. Iron overload and growth of thalassemic patients in marwar region. Int J Pharm Sci Res 2012;3:2043.
21. Saxena A. Growth retardation in thalassemia major patients. Int J Hum Genet 2003;3:237-46.
22. Riaz H, Riaz T, Khan MU, Aziz S, Ullah F, Rehman A, *et al.* Serum ferritin levels, socio-demographic factors and desferrioxamine therapy in multi-transfused thalassemia major patients at a government tertiary care hospital of karachi, pakistan. BMC Res Notes 2011;4:287.
23. Hamidah A, Arini MI, Zarina AL, Zulkifli SZ, Jamal R. Growth velocity in transfusion dependent prepubertal thalassemia patients: Results from a thalassemia center in malaysia. Southeast Asian J Trop Med Public Health 2008;39:900-5.
24. Chhabra GS, Sodhi MK. Pattern of growth retardation and sexual maturation in children having beta thalassaemia. J Nepal Paediatr Soc 2016;36:56-60.
25. Soliman AT, elZalabany M, Amer M, Ansari BM. Growth and pubertal development in transfusion-dependent children and adolescents with thalassaemia major and sickle cell disease: A comparative study. J Trop Pediatr 1999;45:23-30.
26. Berkovitch M, Bistritzer T, Milone SD, Perlman K, Kucharczyk W, Olivieri NF, *et al.* Iron deposition in the anterior pituitary in homozygous beta-thalassemia: MRI evaluation and correlation with gonadal function. J Pediatr Endocrinol Metab 2000;13:179-84.
27. Drema L, Singh P, Singh K, Pannu MS, Kaur M, Neki NS. Thyroid profile in multi transfused children of beta thalassemia major and its correlation with serum ferritin levels. Int J Curr Res Med Sci 2017;3:14-21.
28. Pirinççioğlu AG, Deniz T, Gökalp D, Beyazit N, Haspolat K, Söker M, *et al.* Assessment of thyroid function in children aged 1-13 years with beta-thalassemia major. Iran J Pediatr 2011;21:77-82.
29. Jaipuria R, Nigam RK, Malik R, Shrivastava A, Balani S, Tripathi A. Assessment of thyroid function in children with beta-thalassemia major and its correlation with serum ferritin and transfusion index. J Evol Med Dent Sci 2014;3:847-54.
30. Joshi R, Phatarpekar A. Endocrine abnormalities in children with beta thalassaemia major. Sri Lanka J Child Health 2013;42:81.
31. Sharma S, Dutt N, Sidhu M, Digra S, Meenia R. Prevalence of hypothyroidism, diabetes mellitus and delayed puberty in patients of thalassemia major in a tertiary care center of Jammu province, Jammu Kashmir, India. Int J Adv Med 2017;4:673-7.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Kataki RP, Bharati S. Relationship between serum ferritin and endocrinopathies in thalassemic children: A hospital-based study. Indian J Child Health. 2019; 6(5):201-204.

Doi: 10.32677/IJCH.2019.v06.i05.002